Clinical Neurophysiology 170 (2025) 98–109

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

An objective and sensitive electrophysiological marker of word semantic categorization impairment in Alzheimer's disease

Justine David [a], Lisa Quenon [b], Bernard Hanseeuw [b], Adrian Ivanoiu [b], Angélique Volfart [c], Laurent Koessler [a], Bruno Rossion [a,d,*]

[a] Université de Lorraine, CNRS, IMoPA, 29 Avenue du Maréchal de Lattre de Tassigny, F-54000 Nancy, France
[b] Institute of Neuroscience (IONS) – Université Catholique de Louvain (UCLouvain), Cliniques universitaires Saint-Luc, Neurology Department, Avenue Mounier, B-1200 Brussels, Belgium
[c] School of Psychology and Counselling, Faculty of Health, Queensland University of Technology, Kelvin Grove Campus, QLD-4059, Australia
[d] Université de Lorraine, CHRU-Nancy, Service de Neurologie, 29 Avenue du Maréchal de Lattre de Tassigny, F-54000 Nancy, France

ARTICLE INFO

Keywords:
Alzheimer's disease
Electroencephalography
Fast Periodic Visual Stimulation
Semantic Categorization
Cognitive Biomarkers

ABSTRACT

Objective: Combining electroencephalographic (EEG) recording and fast periodic visual stimulation (FPVS) to provide an implicit, objective and sensitive electrophysiological measure of semantic word categorization impairment in Alzheimer's Disease (AD).
Methods: Twenty-five AD patients and 25 matched elderly healthy controls were tested with a validated FPVS-EEG paradigm in which different written words of the same semantic category (cities) appear at a fixed frequency of 4 words per second (4 Hz) for 70 seconds. Words from a different semantic category (animal) appear every 4 stimuli (i.e., 1 Hz).
Results: Frequency domain EEG analysis showed a robust response objectively identified at specific 1 Hz harmonics over the left occipito-temporal cortex for healthy controls, indexing automatic semantic categorization. However, only a negligible response, less than 25 % of healthy controls', was found in AD patients, this response being inversely correlated with the amount of Tau protein in the cerebrospinal fluid. The significant group difference was maximal when including an additional left central region, with only 2.5 min of testing providing a significant group difference.
Conclusion: A reduced semantic word categorisation EEG amplitude rapidly differentiates AD patients from healthy controls.
Significance: FPVS-EEG provides a valuable electrophysiological index of semantic categorization impairment in AD.

1. Introduction

Methods to measure biological markers of Alzheimer's disease (e.g., Lumbar puncture, Positron Emission Tomography (PET)-FDG, Amyloid-PET…) are well developed and commonly used in clinical practice (see NIA recommendation (Jack et al., 2011)). However, due to their invasiveness and relatively high cost, these biomarkers have limited availability. Most importantly, these biomarkers, such as the level of protein Beta-amyloid in predominantly affected brain structures of the medial temporal lobe, are poor indicators of the severity of cognitive deficits and of the disease's prognosis (Gold et al., 2001; Giannakopoulos et al., 2003; Villemagne et al., 2011). While the ongoing development of blood-based measures promises to provide robust, non-invasive and cost-effective biomarkers (e.g., Teunissen et al., 2022), they will not provide information about cognitive performance. For this reason, developing valid sensitive cognitive measures readily available is of utmost importance for the diagnosis, prognosis, and follow-up of AD patients' cognitive function.

The most currently used approach to evaluate patients' cognitive abilities is neuropsychological evaluation. However, this evaluation relies on explicit behavioural tasks (e.g., Wechsler, 1945; Ivnik et al., 1997; Jacova et al., 2007) that require good oral and written

* Corresponding author at: Imagerie Moléculaire et Physiopathologie (IMoPA) – UMR7365, Pavillon Krug (1er étage - entrée CC-1), Hôpital Central, CHRU Nancy - University Hospital of Nancy, 29 Avenue du Maréchal de Lattre de Tassigny, 54000 Nancy France.
E-mail address: bruno.rossion@univ-lorraine.fr (B. Rossion).

https://doi.org/10.1016/j.clinph.2024.12.018
Accepted 12 December 2024
Available online 16 December 2024

communication abilities and can lead to stress increase, difficulties of task understanding or remembrance (Dorenkamp & Vik, 2018). For these reasons, neuropsychological tests can be challenging to administer in AD patients, especially in the late stages of the disease. Moreover, beyond the affected cognitive function in AD, there is substantial inter- and intra-individual variability in the measures due to attentional, motivational, decisional, and understanding processes (Johansson, 1991; Schretlen et al., 2003; Salthouse, 2007).

An interesting alternative for measuring cognitive function in AD is electroencephalographic (EEG) recording, which can provide implicit direct measures of cerebral activity, non-invasively and at modest costs. However, attempts to develop EEG markers of AD either with resting state measures (Babiloni et al., 2013; Vecchio et al., 2013; Cassani et al., 2018), during sleep (Petit et al, 2004; Hot et al., 2011; Zhang et al., 2019), or with event-related potentials (ERPs) face a number of difficulties in terms of objectivity of identification and quantification of (EEG) activities of interest as well as sensitivity. In particular, while various ERP components (e.g., P300, N400) have been reported as being affected in AD (see Olichney et al., 2001; Joyal et al., 2020; Paitel et al., 2021 for reviews), *meta*-analyses report a high variability of sensitivity between studies (Moore, 1997; Katada et al., 2004; Polich & Corey-Bloom, 2005; Tarawneh et al., 2021), which can be attributed to limitations in objectivity of measurements (Šoškić et al., 2022) as well as low signal-to-noise ratio (SNR). For these reasons, EEG measures are rarely used for diagnosis or prognosis of AD in clinical practice.

Taking into account these issues, the goal of the present study is to provide an objective and sensitive EEG measure with fast periodic visual stimulation (FPVS), contributing to the diagnosis and prognosis of AD patients' cognitive function. The FPVS-EEG approach is based on the early observation in EEG research that a visual stimulus presented at a fixed rate generates an electrical brain response exactly at the stimulation frequency (Adrian & Matthews, 1934). EEG data obtained in these conditions can be transformed in the frequency domain through Fourier analysis (Regan, 1966), providing highly sensitive (i.e., high signal-to-noise ratio, SNR) and objective (i.e., at a pre-determined frequency) quantifiable markers of a visual brain response without explicit task (Regan, 1989; Norcia et al., 2015). These characteristics make this approach ideal to use as a clinical diagnostic tool across age and in different populations (Regan, 1981; Regan, 1989; Rossion, 2014; Norcia et al., 2015; Vettori et al., 2019). While this approach has long been confined to the study of low-level visual processes (i.e., ophthalmology and low-level vision, Regan, 1989; Norcia et al., 2015 for review) as well as their modulation by spatial and selective attention (Morgan et al., 1996; Müller et al., 2006), it has been extended over the last decade to measure visual recognition of complex stimuli such as faces (e.g. Rossion & Boremanse, 2011; Rossion et al., 2020) and written words (Lochy et al., 2015).

In a recent study using this approach (Stothart et al., 2021), various object pictures were presented at a fixed rate of 3 Hz, with the periodic presentation (i.e. every five stimuli, or 0.6 Hz) of a picture previously encoded (named) by the participant. Impressively, following only 9 min of stimulation, there was a significant reduction of the EEG response at the encoded picture presentation frequency (oddball frequency, i.e., 0.6 Hz and harmonics) in AD patients compared to normal controls (Stothart et al., 2021). While these results are highly promising, the effects reported were likely to be due to physical differences between a large set of non-repeated and a small set of highly repeated images as suggested both by topographical localization of the effect and similar findings made without image encoding (Stothart et al., 2021). Thus, whether high(er) level cognitive functions typically affected in AD can be targeted by this FPVS-EEG approach remains unknown.

Capitalizing on these observations the present study directly contrasts AD patients and healthy controls in a recently validated FPVS-EEG paradigm measuring language-related semantic memory (Volfart et al., 2021). Semantic memory, which corresponds to our general knowledge about the world (e.g., concept definition, language, object function…) is widely affected in AD (Hodges et al., 1992; Chertkow et al., 2008) with, in particular, a loss of semantic concepts due to weakened associations between related semantic items (Salmon et al., 1999). Since this deficit is found even at very early stage of the disease (Vogel et al., 2005; Joubert et al., 2010; Caputi et al., 2016), a reliable measure of semantic memory could be valuable to detect abnormalities as early as possible. Importantly, while many behavioural semantic studies with AD have used pictures in denomination or matching tasks, here we used semantic categorization of written words due to their arbitrary mapping between form and meaning (Lambon Ralph et al., 1999; Gasser, 2004). Specifically, we presented written words belonging to the same semantic category at a 4 Hz frequency, with a word belonging to another semantic category appearing every four words (1 Hz). In healthy young individuals, a significant response is observed at the semantic category change frequency (i.e., 1 Hz harmonics) over left-occipito temporal sites following only 4 min of stimulation (Volfart et al., 2021), reflecting participants' semantic categorisation function. Here, with the same paradigm, we hypothesize a significant reduction of this response in AD patients compared to healthy matched controls.

2. Methods

2.1. Participants

Two groups were included in the study: a group of 25 AD patients (mean age: 72.7 ± 7; 16 females) and a group of 25 healthy participants (mean age: 72 ± 6; 15 females) matched for gender and age (Table 1). All participants were Caucasian, native French-speaking living in Belgium. Sample size was determined prior to the beginning of the study, based on patients' availability, the number of participants typically used in FPVS-EEG studies (characterized by a high SNR) (e.g., N = 15 in Volfart et al., 2021) as well as previous EEG studies of AD (e.g., N = 20 in Stothart et al., 2021). Patients were recruited at the memory clinic of Saint-Luc University Hospital in Brussels (Belgium). They were characterised by impaired memory performance at neuropsychological tests (memory z-score < -1.5), either in isolation or in combination with impaired performance in another cognitive domain (language, executive, visuospatial) and a tau/amyloid Beta-42 ratio > 1.2 in the cerebrospinal fluid. Control participants were recruited through mailbox announces in the neighbourhood of the hospital. Inclusion criteria for this group were a MMSE score ≥ 27/30 and cognitive performance in the normal range on the neuropsychological assessment (Z-score > -1.5). Exclusion criteria were non-AD neurodegenerative pathology, focal brain lesions, psychiatric diseases, alcohol, or drug abuse. Two control participants and one AD patient were current smokers. All participants gave written consent before starting the study and the protocol was approved by the ethical committee Eudra-CT 2018–003473-94 of UCLouvain.

2.2. Neuropsychological evaluation

The neuropsychological assessment evaluated four cognitive domains: memory (Free and Cued Selective Reminding Test, French version (Van der Linden et al., 2004)), language (Lexis Naming Test, the Category Fluency Test for animals, and the Letter Fluency Test for the letter 'P' (de Partz et al., 1992)), executive functions (Trail Making Test, Luria's Graphic Sequences (adaptations in French, unpublished)), and visuospatial abilities (Clock Drawing Test and the Praxis part of the CERAD battery (Morris et al., 1988; Rouleau et al., 1992)). A composite score (z-score) was computed based on three measures for each of these domains (for further details about the method, see Ivanoiu et al., 2015), with an independent sample of 32 healthy older individuals who remained cognitively stable over an eight-year period as reference. Two patients did not complete all the tests of the battery due to fatigue and difficulty, as well as five controls due to technical issues.

Table 1
Demographic data of AD patients and control participants.

	AD patients n = 25			Control subjects n = 25			p-value
	Min	**Max**	**Mean (±SD)**	**Min**	**Max**	**Mean (±SD)**	
Age	58	84	72.7 ± 6.64	59	85	72 ± 6.30	ns
MMSE	16	30	23 ± 2.95	27	30	28.8 ± 0.85	$p < 0.000001$
Education level*	***(1)***	***(2)***	***(3)***	***(1)***	***(2)***	***(3)***	
Nb participants	4	3	18	1	2	22	ns
Nb females	16			15			ns
Cognitive measures	**Mean (±SD)**			**Mean (±SD)**			$p < 0.000001$
Memory composite	−4.75 ± 1.6			0.3 ± 0.6			$p < 0.00001$
Executive composite	−1.6 ± 1.5			0.2 ± 0.4			$p < 0.0001$
Visuo-spatial composite	−1.6 ± 1.8			0.2 ± 0.5			$p < 0.00001$
Language composite	−1.6 ± 1.1			0.1 ± 0.6			$p < 0.000001$
Animal Fluency (z-score)	−1.7 ± 1.0			0.2 ± 1.1			$p < 0.000001$
Letter Fluency (z-score)	−1.2 ± 0.8			0.2 ± 0.5			

* (1) = primary education; (2) = secondary education; (3) post-secondary education.

2.3. EEG acquisition

High-density 68-channel EEG was recorded with a BioSemi Active-Two system (Biosemi, Amsterdam, The Netherlands), with a standard (10–20) 64 channels montage completed by 4 electrodes added to occipito-temporal sites (two on the left: PO9, I1; and two on the right: I2, PO10)(Hemptinne et al., 2023). Offsets of the electrodes, referenced to the common mode sense (CMS), were held below 30 μV. Three flat-type Active-electrodes were used to record electrooculogram (EOG): one above the participant right eye and two laterals to the external canthi of the two eyes. The EEG and EOG were digitized at a sampling rate of 512 Hz.

2.4. Stimuli

Stimuli were the same as used in Volfart et al. (2021). Written words from two different semantic categories were selected: animals and cities. Each category was composed of 23 words. Words were written in capital letters (font Verdana) and their length varied between 4 and 8 letters. Stimuli size was of 720 x 540 pixels. Displayed on a computer screen at a distance of 80 cm from the participant, the stimuli subtended a visual angle of approximately 1.6° in height and 5° to 11.8° in width.

2.5. Experimental procedures

The experiment was run in a quiet and low-lit room. Twelve CTR participants and eleven AD patients were testing during the morning and thirteen CTR participants and fourteen AD patients during the afternoon, preventing any biases due to attentional vigilance. After preparing the EEG recording, the participant was seated at 80 cm from a computer monitor. The computer screen had a refresh rate of 120 Hz. The paradigm was adapted from Volfart et al. (2021) to include only the condition giving rise to the largest amplitude for the conceptual categorization response. Written words belonging to the same semantic category (cities) were presented at a frequency rate of 4 Hz and words from the other semantic category (animals) were presented periodically every four images, corresponding to a frequency rate of 1 Hz (4/4) (see Fig. 1). Stimuli were presented through squarewave modulation of contrast, meaning that the contrast went from 0 % to 100 % between each stimulus presentation (Fig. 1A). Stimuli were selected randomly within each category, with no immediate repetition. Each sequence began with 2 to 5 seconds (sec) of grey background and a 2 sec stimulus fade-in, during which the maximum stimulus contrast gradually increased to 100 %, in order to reduce expectation and behavioural reaction (e.g., blinks) to sudden stimulus-onset. Then, the stimuli were presented for 70 sec before 2 sec of fade-out (Fig. 1B). In total, each participant completed 6 sequences (about 7 min of testing).

An orthogonal task was designed to maintain participants' attentional level constant during the experiment. During each sequence, two vertical black bars were presented surrounding the written word, these bars briefly changing colour (for 1 sec, from black to white) either simultaneously or only one at a time (as used in Yan et al., 2022). Participants' task was to attend to the stimuli displayed on the computer monitor and to press on a response box button every time a bar surrounding the image changed colour. These colour changes occurred randomly 8 times within each trial. Performance at detecting the colour change was close to ceiling for both groups (AD patients: 0.95 ± 0.07; control group (CTR): 0.98 ± 0.03). Mean correct Response Times (RT)

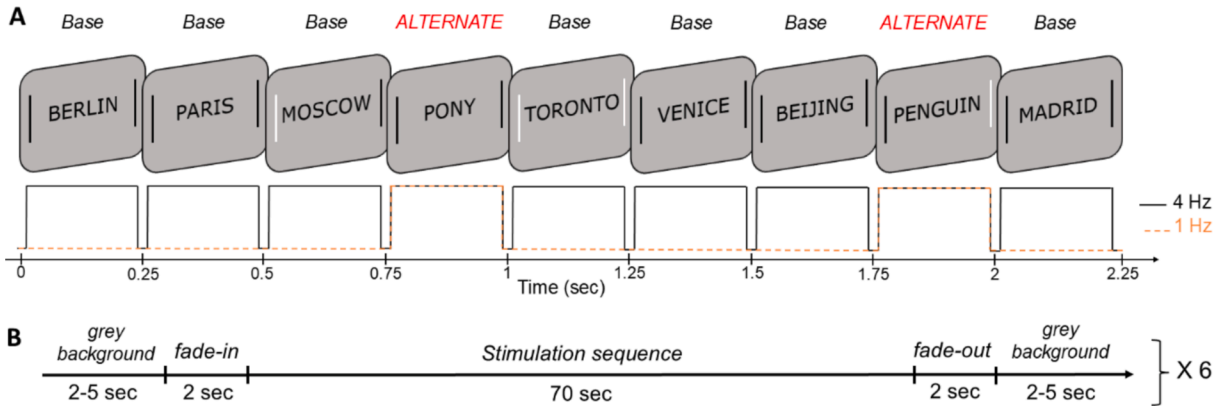

Fig. 1. (A) Schematic representation of the experimental paradigm. City names were presented at 4 Hz, except every four words where an animal name was presented (i.e., change of semantic category at 1 Hz). The vertical bars change colour at random times for the orthogonal task. (B) A stimulation sequence starts with 2 to 5 sec of grey background and a 2 sec stimulus fade-in, then the stimulation sequence lasted for 70 sec and end with 2 sec of fade-out and 2 to 5 sec of grey background. Each participant completed 6 sequences (about 7 min of experiment).

(AD patients 0.54 ± 0.0.22 sec; CTR: 0.48 ± 0.07 sec) did not differ between groups (U = 341, p = 0.59).

2.6. EEG analysis

EEG analyses were performed in Letswave 6, an open-source toolbox (https://www.letswave.org/) running over MATLAB R2021a (MathWorks, USA). Data processing steps were similar to previous FPVS-EEG studies (e.g., Rossion et al., 2020; Volfart et al., 2021, David et al., 2023) but are also detailed below.

First, a single EEG data file was imported for each participant. The data were then filtered using a Butterworth band-pass filter with a cut-off value of 0.1–100 Hz, and a Fast Fourier Transform (FFT) multi-notch filter with a width of 0.5 Hz to remove electrical noise at 50 Hz frequency and 2 harmonics (100 and 150 Hz). After being downsampled to 256 Hz to reduce computational load and storage space, data were segmented by sequence, including 2 sec before and after the sequence (−2 to 74 sec). One sequence was removed for one AD patient because the EEG was too noisy. Eyeblink correction was applied on participants who blinked more than 0.2 times/sec on averaged during the sequence (Retter & Rossion, 2016) with independent component analysis (ICA, Jung et al., 2000; Joyce et al., 2004), removing only one clear component (in 19 AD patients and 11 CTR participants). Considering the larger number of AD patients with ICA correction compared to controls, we also conducted analyses without any ICA correction, with no difference in conclusions (results presented in Supplementary Figure 1). Individual channels with artifacts (0–3 channels per participant; 1.2 % of channels on average for AD patients and 0.7 % for CTR) were interpolated with linear combination of three neighbouring channels. All EEG channels were re-referenced to a common average reference. Each sequence was then re-segmented to an integer number of 1 Hz cycles, excluding fade in and fade out stimulation portions. The resulting cropped epochs were 70 sec long and contained exactly 280 cycles of 0.25 sec. Epochs were averaged in the time-domain for each participant to increase signal-to-noise ratio. Then, a Fast Fourier Transform (FFT) was applied, and the amplitude spectra were extracted, with a high frequency resolution of 0.0143 Hz (1/70 sec).

The main Regions Of Interest (ROI) were pre-defined based on the results of the study of Volfart et al. (2021), taking into account the lower number of channels used in the present study (68 vs. 128): a left occipito-temporal region (LOT) composed of 6 contiguous electrodes (P7, P9, PO7, PO9, O1, I1) and a bilateral occipital ROI for the base frequency response (12 contiguous electrodes: P7, P9, PO7, PO9, O1, I1, P8, P10, PO8, PO10, O2, I2). In order to identify significant responses at the frequency of interest and harmonics, we calculated Z-scores (Z = (x-μ baseline noise) / σ baseline noise; x being the amplitude of the bin of interest) across the ROI of the FFT spectrum average across individuals. The baseline noise level was estimated as the average of twenty-two surrounding bins, excluding the immediately adjacent bins (i.e., 10 frequency bins on each side, corresponding to a frequency range of 0.3146 Hz). Responses were considered significant if the Z-score was above 1.64 ($p < 0.05$), indicating that the response was significantly larger than the EEG noise estimated in the neighbouring frequencies.

To quantify the response, significant harmonics of frequency of interest identified in the previous step were summed (Retter & Rossion, 2016; Retter et al., 2021). For that, the EEG spectrum was segmented into successive chunks centred on the bin containing the conceptual categorisation frequency (1 Hz, 2 Hz, 3 Hz, etc.) and chunks of significant harmonics were summed. Each chunk contained 25 bins (i.e., a chunk length of 0.357 Hz) to provide a good estimation of noise without any overlap between harmonics. Then, two methods were used to quantify the response based on validated previous studies (see Norcia et al., 2015; Rossion et al., 2020): (1) subtraction of the baseline activity from the signal (corrected amplitude in μV), (2) ratio of the baseline to the signal (signal to noise ratio, SNR) for visualization. Baseline EEG activity was estimated as the average of twenty-four surrounding bins excluding the immediately adjacent bins and the local maximum and minimum amplitude bins (i.e., 10 frequency bins on each side). Grand average spectra were computed to display results at the group level.

The number of significant electrodes was also calculated for each participant and at the group level by computing Z-scores on each electrode amplitude for every individual.

2.7. Statistical analyses

Statistical analyses were performed with RStudio. Student t-tests were computed to compare amplitude of the response between groups. When the data did not validate parametric test conditions (i.e., normal distribution), Wilcoxon-Mann-Whitney tests were used. Bonferroni correction was applied to control for multiple comparisons. To test correlations between EEG amplitude response and other biomarkers, Pearson correlations were computed for normally distributed data, and Spearman correlations for data violating the assumption of normality. To determine the classification power of the EEG measure, a receiver operator characteristic curve (ROC) was calculated. Finally, chi-squared tests were used to compare the proportion of significant electrodes between groups.

3. Results

3.1. Semantic categorization response (1 Hz and harmonics) at the group level

At the group level, there was a marked contrast between CTR and AD patients: while clear-cut responses were observed at several harmonics of the 1 Hz semantic category alternate stimulation frequency (e.g., 2 Hz, 3 Hz, 5 Hz…) over the LOT ROI for CTR, extending Volfart et al. (2021)'s results to older participants, this response was barely visible in AD patients' group on the SNR spectra (Fig. 2A). As in Volfart et al. (2021), the response at the fundamental frequency of 1 Hz, or first harmonic, over the LOT ROI was not significant in either of the two groups (Z = 1.60 in CTR; Z = -0.09 in AD, $p > 0.05$). However, in the CTR group, responses at 4 harmonics of 1 Hz were highly significant (i.e., 2 Hz: Z = 7.4, 3 Hz: Z = 9.6, 5 Hz: Z = 4.0 and 6 Hz: Z = 4.7, all p's < 0.001), with no harmonic being significant at the threshold of $p < 0.001$ in AD patients' group. At lower thresholds, only one or two harmonics were significant for AD patients' group (i.e., 2 Hz: Z = 1.5, $p > 0.05$, 3 Hz: Z = 1.9, $p < 0.05$,5Hz: Z = 2.9, $p < 0.01$ and 6 Hz: Z = 1.3, $p > 0.05$). Grand-averages topographical maps show the peak's response over the LOT region in CTR, as expected (Fig. 2C), without much response in the AD group. Importantly, there was no evidence of a mere change of scalp topography, e.g., with another region or set of electrode(s) showing a larger response in AD than CTR. Instead, a second region with a clear response, over left central electrodes, was found in CTR, with no visible response in the AD patients' group (Fig. 2C).

The large group difference observed over the LOT ROI was confirmed by the sum of harmonics (1 to 6 Hz, excluding 4 Hz; see supplementary material Fig. 2 for analyses without including the 1 Hz harmonic response, and no change in results), with a baseline-corrected response reaching 0.45 μV for CTR, and only about 0.09 μV for AD patients (Fig. 2B). While the overall response over the LOT ROI reached significance for AD patients' group (Z = 2.6, $p < 0.01$; SNR = 1.2 ± 0.3), the level of statistical significance was much higher for the CTR group (Z = 8.8, $p < 0.001$; SNR = 1.4 ± 0.4). Over the LOT region, AD patients' average response amplitude was significantly lower than the CTR group's response ($t_{48} = 2.18$, $p = 0.03$, $d = 0.62$) (Fig. 2B & Fig. 3A).

In order *to* define the most sensitive contrast between groups a posteriori (i.e., based on observations of the present study), *we* also compared AD patients to CTR on a central (CT) ROI composed of 6 central electrodes (FCz, Cz, CPz, CP1, C1, FC1), as well as a combination of CT and LOT ROIs (Fig. 3C&D). The response at the left CT region was significant for both groups, with a highly significant response for the

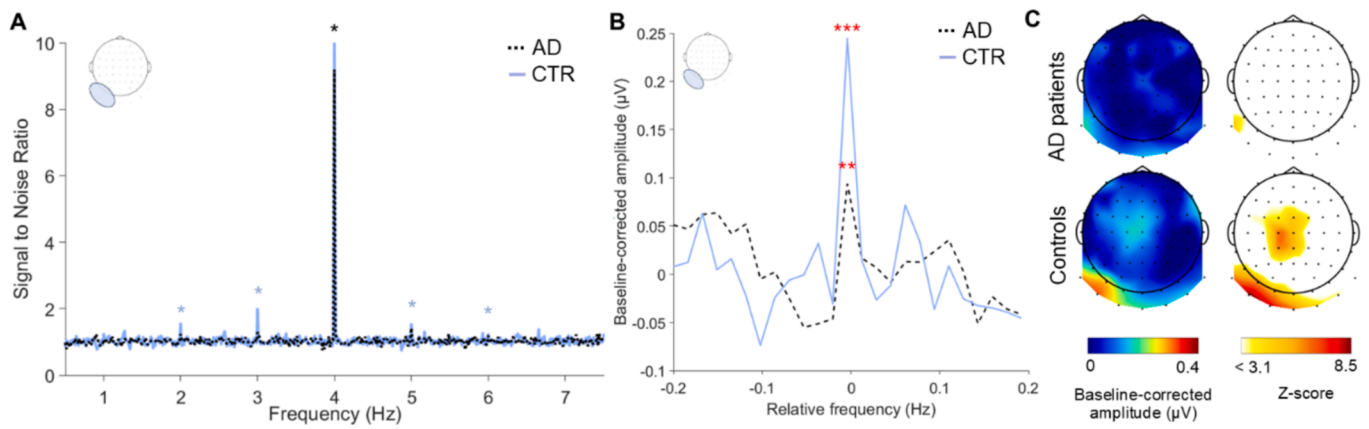

Fig. 2. (A) Grand-averaged FFT spectra (SNR) at the LOT ROI. Black asterisks indicate significant responses for both groups while blue asterisks indicate responses significant only for the CTR group ($p < 0.001$). While the semantic categorization response may appear relatively weak relative to the 4 Hz base rate stimulation, it is in fact associated with high SNR (e.g., third harmonic at 3 Hz, SNR = 1.98, corresponding to 98 % increase in signal).(B) Baseline-corrected amplitude of the sum of the five first oddball harmonics at LOT ROI. The spectrum is centred on the frequency bin of interest (***=$p < 0.001$; **= $p < 0.01$). (C) Scalp map topographies of the corrected amplitude response (on the left) averaged across participants at the semantic category change frequency (1 Hz and harmonics) for AD patients and controls groups. Scalp map topographies of significant Z-scores responses are presented on the right (white = non-significant response). Note the clear response at the central region also observed for the CTR group but not for AD group.

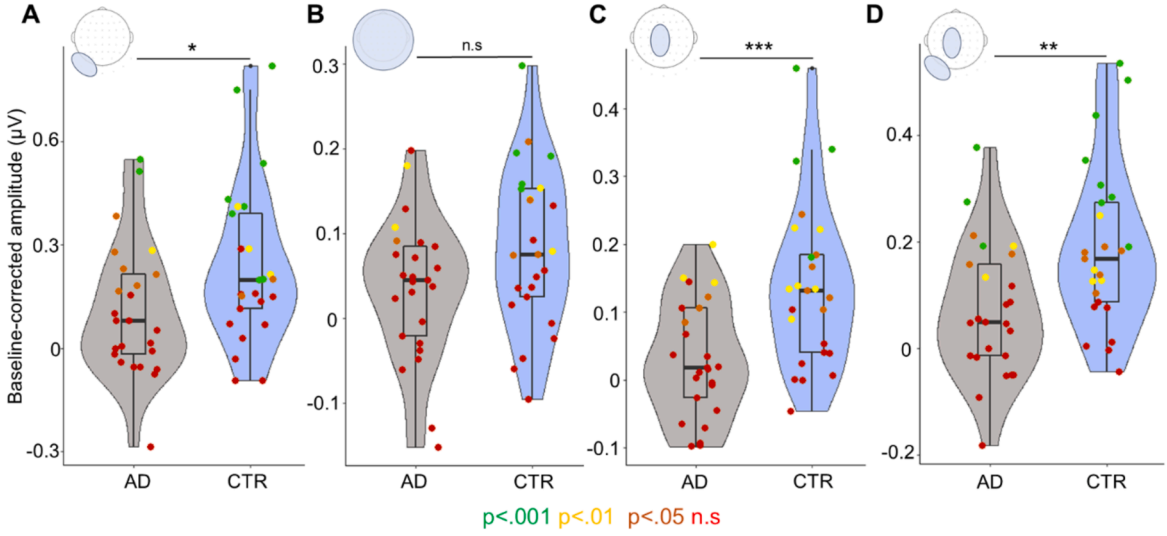

Fig. 3. Violin plot and boxplot of corrected amplitude response at the sum of oddball frequency and harmonics for (A) LOT region (i.e., 6 electrodes), (B) average of all the 68 electrodes, (C) CT region (i.e., 6 electrodes), (D) a combination of LOT and CT regions (i.e., 12 electrodes) for AD patients in grey and CTR group in blue. Each dot representing one participant, the colour of the dot represents significance level of each individual response across considered electrodes (green: $p < 0.001$, yellow: $p < 0.01$, orange: $p < 0.05$, red: n.s). The largest significant difference between groups is found for the central region (*: $p < 0.05$; **: $p < 0.01$; ***:$p < 0.001$).

CTR group ($Z = 6.9$, $p < 0.001$) but a response just above the significance level for AD patients ($Z = 1.7$, $p < 0.05$)(Fig. 2C). Despite an overall lower response (SNR in CTR:1.3 ± 0.2; AD:1.07 ± 0.2), the discriminative power of the central region ($t_{48} = 3.63$, $p = 0.0007$, $d = 1.03$) was higher than the LOT region. Combining the 2 regions did not enhance discriminative power ($t_{48} = 2.99$, $p = 0.004$, $d = 0.85$). Note that there was a strong correlation between the amplitude response of the LOT and CT regions for both groups (AD: $r = 0.59$, $p = 0.004$; CTR: $r = 0.45$, $p = 0.02$). The best classification performance of the EEG measure to discriminate AD from CTR was found using SNR at the CT ROI (AUC = 0.79, 95 % confidence interval: 0.66 – 0.91, $p = 0.0005$, see supplementary material Fig. 3).

We also identified the number of significant electrodes at the group level at a threshold of $Z > 3.1$ ($p < 0.001$). In the CTR group, there were 19 significant electrodes (grouped in two contiguous clusters, Fig. 2C), which is well above chance level (i.e., 68*0,05 = 3,4)($p < 0.001$). In the group of AD patients, there was only 2 significant electrodes (Fig. 2C), i.e., not above chance level. The proportion of significant electrodes was significantly higher in CTR than AD patients ($\chi^2 = 14.4$, $p < 0.00001$). At a less conservative threshold p-value ($Z > 1.64$, $p < 0.05$), 40 electrodes were significant for the CTR group ($p < 00001$) compared to 8 for AD patients' group ($p = 0.13$), also resulting in a highly significant difference between groups ($\chi^2 = 30.9$, $p < 0.00001$).

As a final analysis at the group level, we compared groups of CTR and AD patients in terms of the evolution of response across the 6 stimulation sequences. While there was no significant difference between groups after only 1 sequence ($U = 267$, $p = 0.39$, $d = 0.39$), the difference was already highly significant after the second sequence ($t_{48} = 3.75$, $p = 0.0005$, $d = 1.06$), remaining stable with additional sequences (Fig. 4).

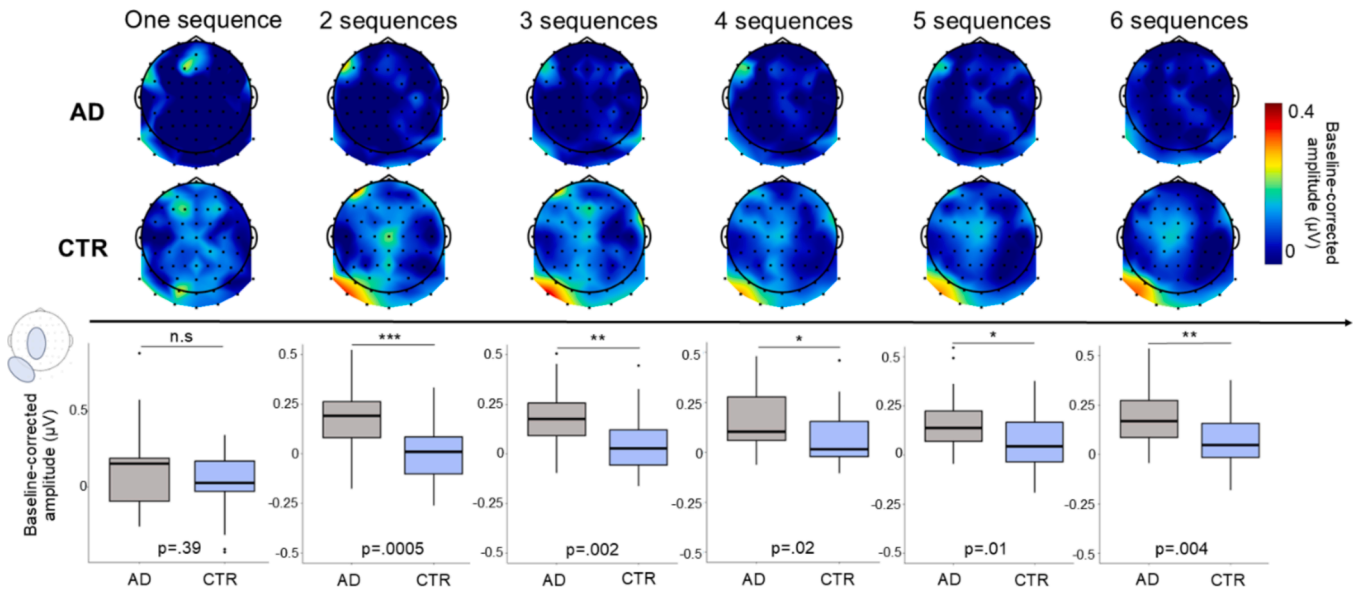

Fig. 4. Boxplot of the amplitude response at the sum of oddball frequency for the combination of LOT and CT regions with sequence cumulation (beginning on the left with only 1 sequence, followed by the first two sequences, the first three sequences, etc…). P-values of t-tests comparing the two groups are indicated for each cumulation of sequences. A significant difference between groups is found already after the second stimulation sequence (*: $p < 0.05$; **: $p < 0.01$;***: $p < 0.001$). Scalp map topographies of the corrected amplitude are presented above.

3.2. Semantic categorization response at the individual level

The frequency-domain data obtained during FPVS allows to perform a straightforward statistical analysis at the individual level, using the distribution of noise EEG activity in the neighbouring bins of the frequencies of interest for each individual (e.g., Lochy et al., 2015; Rossion et al., 2020). At the individual level, 13 CTR and 9 AD patients had a significant response ($Z > 1.64$, $p < 0.05$) over the LOT region (no significant difference in proportion between groups: $\chi^2 = 0.73$, $p = 0.2$, Fig. 3A). The contrast was stronger on the central region, with 16 CTR showing a significant response, for only 6 AD patients ($\chi^2 = 6.57$, $p = 0.005$, Fig. 3C). A similar contrast was found with the combination of the 2 regions (18 CTR and 8 AD patients, $\chi^2 = 6.49$, $p = 0.005$, Fig. 3D). Taking a more conservative threshold ($Z > 2.32$, $p < 0.01$), only 4 AD patients showed a significant response against 11 CTR at the LOT ROI ($\chi^2 = 3.43$, $p = 0.03$), and only 10 controls against 3 AD patients at CT ROI ($\chi^2 = 3.74$, $p = 0.03$) and 12 controls against 5 AD patients at the combination of LOT and CT ROI ($\chi^2 = 3.21$, $p = 0.04$).

We also considered the number of significant electrodes for each individual (with FDR correction). There were only 4/25 AD patients with at least four significant electrodes (chance level = 3.4), against 15/25 CTR ($\chi^2 = 10.03$, $p = 0.0008$) (Fig. 5 & Fig. 6). The number of significant electrodes by participant was also much higher in CTR than AD patients (CTR: 8.44 ± 8.71, AD: 2.32 ± 4.7, $p < 0.01$, Fig. 6).

Finally, EEG amplitude responses summed across harmonics at LOT ROI were not correlated with performance at the orthogonal task (RT and Accuracy (Acc)) for any of the groups (AD patients: RT: r = -0.18, p = 0.38, Acc: r = 0.06,p = 0.78; CTR: RT: r = 0.10,p = 0.64, Acc: r = -0.26,p = 0.20).

3.3. General visual base rate response (4 Hz and harmonics)

A clear EEG response at 4 Hz and harmonics was found for both groups, maximally localized over the bilateral occipito-temporal region (*Supplementary Figure 4*). The response was significant until the tenth harmonics (40 Hz) for the CTR group but only until the eighth harmonics (32 Hz) for the group of AD patients. All individual participants had a significant amplitude response at the base frequency at bilateral occipito-temporal ROI (all ps'<0.01, *Supplementary Figure 4*). Analyses were run with the sum of the first ten harmonics for both groups, and also with only the significant harmonics defined independently for each group (i.e., 10 for CTR and 8 for AD patients). At the bilateral occipito-temporal region, the response was highly significant both for the CTR group ($Z = 135.9$, $p < 0.001$) and the AD patients group ($Z = 105.2$, $p < 0.001$).There was no significant difference in amplitude response between groups (AD patients: 1.38 ± 0.8 µV; CTR: 1.80 ± 0.9 µV; $t_{48} = 1.70$, $p = 0.10$, $d = 0.48$). The same results were found when considering only the (8) significant harmonics for the AD patients group (AD patients: 1.37 ± 0.8 µV; $t_{48} = 1.74$, $p = 0.09$, $d = 0.49$).

3.4. Correlation with other AD biomarkers

3.4.1. Neuropsychological tests

Correlations were computed between the amplitude of the semantic categorization response and neuropsychological evaluation scores. With the combination of CT and LOT regions and considering both groups altogether, significant correlations were found with the MMSE, memory test composite score, executive functions composite score, language composite score, animal fluency test score, picture denomination test score, visuo-spatial function composite score and global cognitive score (all p-values and r correlation index are reported in Table 2). However, when computing correlations for each group separately, no significant correlations were found with any of the neuropsychological scores for any of the groups (Table 2, all p's > 0.05).

Concerning the general visual base rate response, AD patients' response at 4 Hz was significantly correlated with the executive functions composite score ($r = 0.48$, $p < 0.05$), the language composite score ($r = 0.44$, $p < 0.05$), the visuo-spatial functions composite score ($r = 0.44$, $p < 0.05$), the animal fluency test score ($r = 0.50$, $p < 0.05$), the picture naming performance ($r = 0.51$, $p < 0.01$) and the global cognitive score ($r = 0.47$, $p < 0.05$). The CTR group's base rate amplitude response was not correlated with any of the neuropsychological scores (all p's > 5; see supplementary material Table 1).

Finally, no significant correlation was found with age, neither for AD patients ($r = 0.16$, $p = 0.44$) nor for CTR ($r = 0.1$; $p = 0.65$).

3.4.2. Cerebrospinal fluid marker

A significant negative correlation was found between the EEG

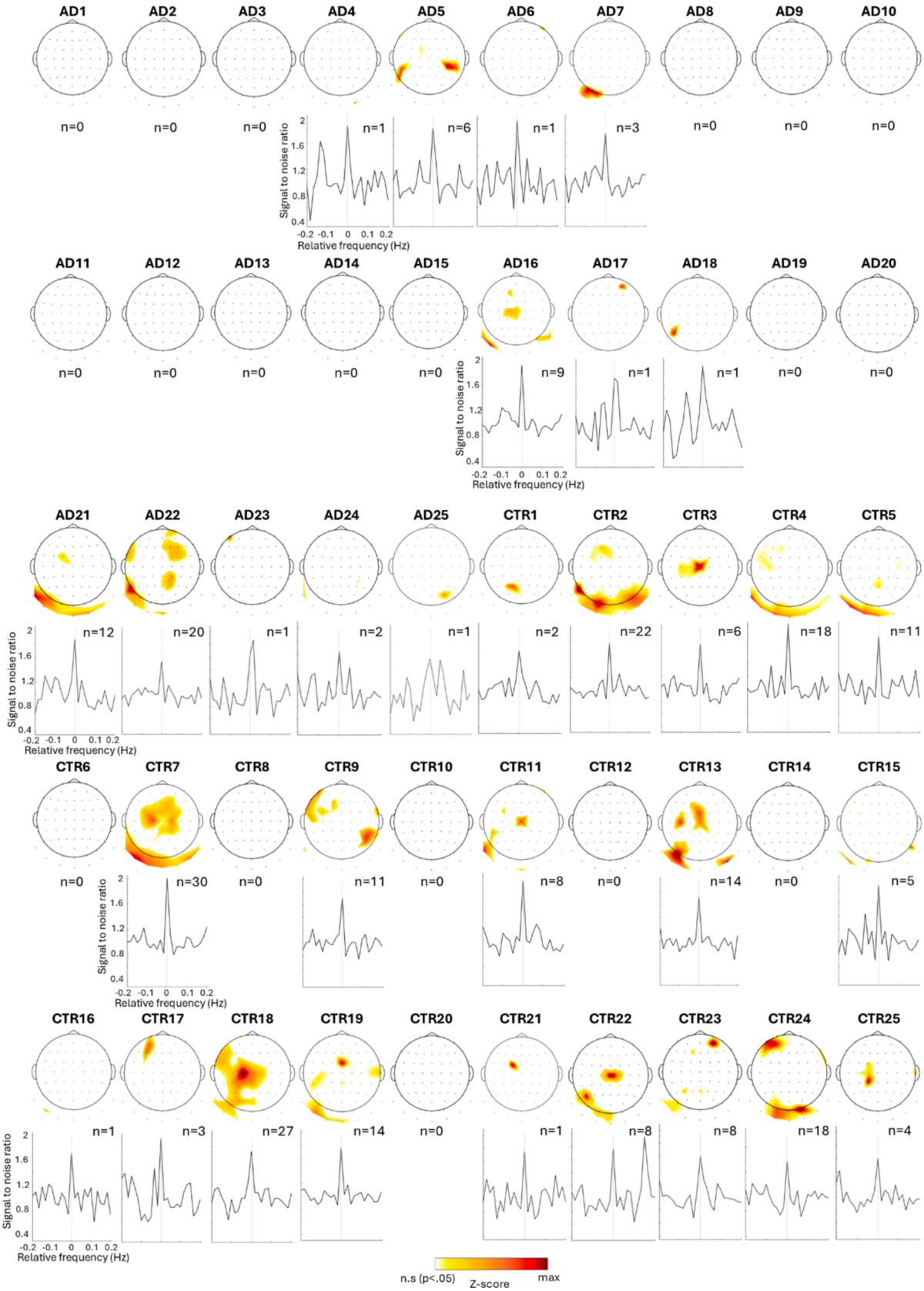

Fig. 5. Individual scalp map topography of significant Z-scores distribution for each participant with FDR-correction. White corresponds to non-significant response. Below each topography the spectrum of the SNR averaged across all significant electrodes by individual participant. The spectrum is centred on the frequency bin of interest, with 0 corresponding to the sum of the oddball frequency (1 Hz) and harmonics. The grey line represents the localisation of the frequency of interest. The number of significant electrodes is indicated for each participant (n).

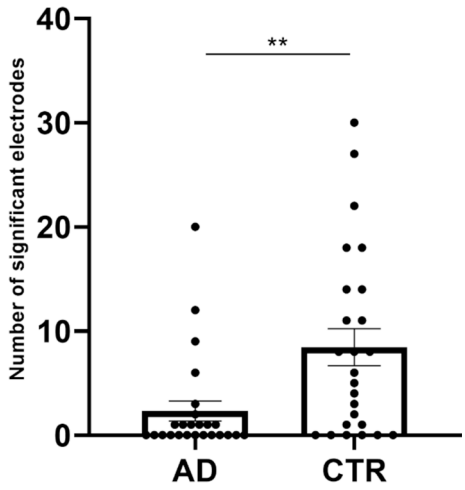

Fig. 6. Boxplot representing the number of electrodes with a significant amplitude at the alternate frequency (1 Hz) for each group. Each dot represents one participant.

Table 2
Correlation between semantic categorization EEG amplitude response (1 Hz and harmonics) and neuropsychological tests scores. Correlations were computed using data of both groups (in the first column), and for AD patients and control group separately (in second and third column). EEG response was quantified across the combination of LOT and central region. Correlations were computed using Pearson correlation when the distribution was normally distributed and Spearman correlation if not. Correlation that survived Bonferroni correction for multiple comparison are presented in bold.

	All		AD		CTR	
	r	p-value	r	p-value	r	p-value
MMSE	0.36	0.009 (**)	−0.05	0.81	0.28	0.17
Memory test (composite score)	0.48	**0.0006 (***)**	0.26	0.24	0.37	0.06
Executive functions (composite score)	0.33	0.02 (*)	0.20	0.37	−0.08	0.70
Language (composite score)	0.40	**0.005 (**)**	0.13	0.55	0.11	0.66
Animal fluency	0.36	0.0098 (**)	0.21	0.32	0.08	0.70
Pictures denomination	0.30	0.04 (*)	0.12	0.57	0.08	0.70
Visuo-spatial functions (composite score)	0.39	0.008 (**)	0.29	0.17	−0.01	0.96
Global cognitive score	0.50	**0.0007 (***)**	0.26	0.23	0.22	0.36

response for semantic categorization and AD patients' cerebrospinal fluid total tau protein level (r = -0.41; p = 0.047). No significant correlation was found with the CSF amyloid-beta 42 level (r = -0.10; p = 0.63).

4. Discussion

Within a few minutes of recordings with an original FPVS-EEG approach, our study demonstrates a large and highly significant reduction of a neural index of semantic categorization in a group of AD patients compared to matched controls.

The control group observations replicate those of Volfart et al. (2021), extending them to the elderly population. As in this previous study, the first harmonic of the semantic categorization response at 1 Hz was not significant, which can be due to two factors. First, the 1 Hz frequency falls in the low frequency range of the EEG spectrum, characterized by a high noise level. Second, the shape of the oddball response may not be well accounted for by a 1 Hz sinewave (e.g., a bi-phasic response of half a second or less, Zhou et al., 2016; Retter et al., 2021). However, and most importantly, 4 related harmonics non-overlapping with the base rate response (i.e., 2 Hz, 3 Hz, 5 Hz and 6 Hz; Fig. 2) were highly significant for the control group, reflecting a high amplitude response specific to word semantic categorization. In contrast, at lower statistical thresholds, only one to two harmonics were significant for AD patients, resulting in an almost negligible group level semantic categorization response.

While the precise nature of AD patients' EEG semantic categorization deficit found here remains speculative, these results are in line with semantic memory deficits present in AD in general (Giffard et al., 2005; Rogers et al., 2006; Wierenga et al., 2011) and with behavioural studies showing higher deficit for semantic categorization of written word than pictures (Montanes et al., 1996; Caputi et al., 2016). The present observations are also in line with the reduction of the central N400 component elicited by semantically inappropriate words in AD compared to controls (Iragui et al., 1996; Castañeda et al., 1997; Ostrosky-Solís et al., 1998; Revonsuo et al., 1998). Here, the EEG response was, as expected, maximally present for both groups at left OT sites, which is consistent with the study of Volfart and colleagues (2021) and with neuroimaging studies showing a strong involvement of the left temporal region in semantic processing of words (e.g., Marinkovic et al., 2003; Rice et al., 2015). Although AD neuropathology first develops in the medial temporal lobe, it extends rapidly to all temporal cortex (Braak & Braak, 1991; Whitwell et al., 2007). Therefore, the reduction of EEG semantic categorisation amplitude response for AD patients is likely to be related to AD patients' temporal lobe neurodegeneration. Gray matter loss (Thompson et al., 2003) leading to weaker postsynaptic synchronization, glucose hypometabolism (Mosconi, 2005) and tau pathology (Ossenkoppele et al., 2016) found in AD patients' temporal lobe could play a role in this reduction of neural response to semantic categorization change. This would be in line with AD group studies showing a link between left temporal region hypoactivation and AD patients' semantic processing deficit (Grossman et al., 2003; Nelissen et al., 2007; Melrose et al., 2009; Libon et al. 2013) and more particularly with the anterior-temporal lobe (ATL) atrophy (Joubert et al., 2010; Frings et al., 2011; Domoto- Reilly et al., 2012; Berron et al., 2020), a region largely involved in semantic processing (Lambon Ralph et al., 2017).

Interestingly, a slightly left-lateralized central region was also significant in the control group but not for AD patients, and quantification of the response in this central region even provided the highest discrimination index between groups. Semantic-specific activity over this central region is in line with ERP studies that have shown the largest N400 component at centro-parietal recording sites (Kutas & Hillyard, 1980; Bentin, 1989; Nigam et al., 1992; Kutas & Federmeier, 2011; Meyer et al., 2024). Moreover, Ford et al. (2001) also found a difference related to age on scalp distribution of the N400 ERP, with a much more distributed response for young individuals and a response focused on central parietal sites only for elderly individuals. Note that although the N400 component is recorded at centro-parietal sites, it is thought to be generated by temporal cortical sources (e.g., Halgren et al., 2002). Hence, the absence of this central response in the AD group can also certainly be related to AD patients disrupted temporal lobe activity as mentioned above.

Importantly, compared to previous behavioural and electrophysiological studies, the present study presents several advantages for the clinical use of FPVS-EEG as a measure of semantic categorization, and cognitive function in general. First and foremost, the highly significant difference between groups was found within only about 7 min of testing and was in fact already significant with only two stimulation sequences (i.e., approximately 2.5 min of testing). This impressive result is due to the high sensitivity of the FPVS-EEG approach, attributed both to the

high number of (semantic) discrimination trials presented in a very short time (i.e., 70 trials by sequence at 1 Hz, for a total of 420 trials over 6 sequences) and to the concentration of all of the signal of interest in tiny frequency bins (0.0143 Hz bandwidth) affected by a small fraction of the broadband EEG noise (see Regan, 1989; Rossion et al., 2020).

A second advantage lies in the objectivity of the approach, with the analysis restricted to pre-defined frequency bins of interest from which a summed EEG amplitude can be readily derived. Thus, the FPVS approach avoids the pitfalls of standard EEG studies (i.e., ERPs or spontaneous/evoked oscillations) with subjective measures often requiring expertise at identifying and quantifying EEG responses, leading to substantial variability across experimenters' measures and studies.

Thanks to these advantages, statistical results can be readily derived at the individual level with the present approach, showing that the FPVS-EEG semantic categorization response is already a good indicator of non-AD. Indeed, based on our observations, there is low probability that a participant with a high amplitude response at the semantic categorization frequency would be an AD patient, as only a very few patients had a high amplitude response. Admittedly, the use of this measure at the individual level remains limited by the high inter-individual variability in response amplitude among control participants, with some control participants also having a very low response amplitude. Correlation analyses suggest that this variability is not due to age or cognitive variables here (see also Volfart et al., 2021). One potential factor accounting for this variability could be differences in control participants' level and speed of semantic comprehension and reading, and future studies measuring those factors will be welcome to better understand this variability. At the individual level still, the number of significant electrodes also strongly discriminate between individuals of the two groups, with only very few AD patients having several significant electrodes, independently of the localization. Sensitivity at the individual participant level could be further improved in the future by testing different stimulation and quantification parameters (e.g., stimulation speed and sequence duration), and by combining this measure with biological markers (e.g., CSF, PET-Amyloid, blood-based biomarkers…). To improve the discriminative power of the measure, the semantic category of the presented words could also be modified, since several studies have shown that AD patients are more impaired for some semantic categories than others, in particular between living and non-living items (Silveri et al., 1991; Lambon Ralph et al., 1997; Garrard et al., 1998; Chan et al., 2001; Hernandez et al., 2008). Finally, semantic distance between the two categories could also be modified, with the hypothesis that alternate words more closely semantically related to the repeated semantic category could be even more complicated to categorize for AD patients (Glosser et al., 1998; Laisney et al., 2011; Passafiume et al., 2012) allowing to detect subtle semantic impairment at earlier disease stages.

A third advantage of the present approach is that the difference observed here between groups was obtained during the realization of a simple orthogonal task, well performed by all participants including AD patients. Hence, the substantial difference in EEG response between groups cannot be attributed to external factors (e.g., stress, task understanding) and processes (e.g., reduction of attention, motivation, decision making, response execution). This is also supported by AD patients showing a robust base stimulation rate response (4 Hz and harmonics), which, despite partly reflecting word-related processes, was not even significantly lower than in CTR group. Together with their normal performance at the orthogonal task, this indicates that AD patients' largely reduced semantic categorization response is not due to a lack of attention to the visual stimulation or failure to generate periodic electrophysiological responses to rapid visual stimulation in general.

As a last advantage of this approach worth mentioning, we note that the semantic categorization response is focal and quite consistent across individuals, so that it could be measured with only a few channels in clinical practice.

Interestingly, there were no significant correlations between neuropsychological tests and the semantic categorization EEG amplitude response within the AD patients' group. This could be explained by the absence of neuropsychological measure focusing on written word semantic categorization, with only semantic verbal fluency and picture naming ability being assessed here. Moreover, as mentioned above, neuropsychological measures are likely to be influenced by factors unrelated to the measured function (e.g., speech production abilities, motivational factors, understanding of instructions…). Finally, and perhaps most importantly, the low variability in the EEG amplitude response in the AD patients' group could also explain this absence of correlation, and future studies performed with participants along the AD clinical spectrum could possibly demonstrate significant correlations. Of note though, the EEG semantic categorization amplitude response of AD patients was correlated with the amount of Tau protein, but not amyloid, in the cerebro-spinal fluid. This is consistent with the fact that protein Tau is a better predictor of cognitive measures than amyloid (Nelson et al., 2012; Brier et al., 2016; Ossenkoppele et al., 2019).

Overall, our results significantly extend those of a recent study (Stothart et al., 2021) showing the potential of FPVS-EEG to discriminate groups of AD patients and CTR individuals within a few minutes of testing. Importantly, our study is original at several levels. First, as mentioned above, that previous study did not find any difference related to picture encoding, suggesting that the effect measured reflects lower-level cognitive processes (i.e., the detection of physical differences between a large set of non-repeated and a small set of highly repeated images). In comparison, the present paradigm isolates a higher-level cognitive function (i.e., semantic categorization) with written words, which allows to remove the influence of physical differences between stimuli. Moreover, this word semantic categorization paradigm did not involve any explicit task before or after the FPVS-EEG recording, preventing biases related to behavioural tasks. Finally, quantification of the EEG response was performed here by summing the response at significant harmonics, which has been demonstrated as the most valid approach (Retter & Rossion, 2016; Retter, Rossion & Schiltz, 2021).

One obvious limitation for the clinical use of the present type of semantic categorization test is that presented words are culture-dependent (e.g., not everybody is familiar with the city names used). However, this paradigm could be easily adapted in other cultures or languages. Another potential limitation of the current study is the limited sample size (N = 25 by group). However, as mentioned in the methodological section, the number of participants is in the range of EEG studies of AD, in particular the only previously reported FPVS-EEG study with AD patients (N = 20 in Stothart et al., 2021), and is higher than the number of participants typically included in FPVS-EEG studies of cognition (usually N = 12–20; e.g., Rossion & Boremanse, 2011; Lochy et al., 2015; Stothart et al., 2021; Volfart et al., 2021). This is because, as mentioned above, EEG responses obtained during this fast periodic stimulation mode present with a very high SNR compared to standard approaches.

Despite our promising results, since this is the first study to evaluate semantic categorization abilities of AD patients with this approach, future studies are needed to progress further towards a clinical use of this approach. First, the specificity of the measure will have to be assessed by testing it in different clinical populations. In the same vein, to ensure that this effect is function-specific, future studies should investigate whether similar FPVS-EEG paradigms measuring cognitive functions that are not impaired in AD show typical responses in these patients (e.g., low-level visual oddball paradigms: contrast variations or gratings orientation changes; Heinrich et al., 2009). Second, its diagnostic value should be evaluated at earlier stages of the disease and the prognostic value will have to be assessed with longitudinal studies. Lastly, considering the high inter-individual variability of the EEG measure found in both groups, it is clear that this measure cannot be considered, at present, as being self-sufficient and could be very informative in association with physiological AD biomarkers that do not

measure cognition (i.e., blood-based biomarkers, CSF biomarkers) to monitor patients' cognitive level.

5. Conclusions

The semantic words categorisation FPVS-EEG amplitude response strongly differentiates a group of AD patients from healthy controls, with a significantly lower EEG amplitude for AD patients. This FPVS-EEG paradigm offers a promising implicit, objective, and sensitive measure of semantic processes deficit in AD.

6. Ethics approval and consent to participate

All participants gave written consent before starting the study and the protocol was approved by the ethical committee Eudra-CT 2018–003473-94 of UCLouvain.

Funding

This research was supported by an ANRT CIFRE PhD fellowship (n°2021/0405) to JD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank Lara Huyghe and Yasmine Salman for their help during EEG data acquisition, and three anonymous reviewers for their constructive criticisms of a previous version of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2024.12.018.

References

Adrian, E.D., Matthews, B.H., 1934. The Berger rhythm: potential changes from the occipital lobes in man. Brain 57 (4), 355–385.
Babiloni, C., Del Percio, C., Bordet, R., Bourriez, J.L., Bentivoglio, M., Payoux, P., Rossini, P.M., 2013. Effects of acetylcholinesterase inhibitors and memantine on resting-state electroencephalographic rhythms in Alzheimer's disease patients. Clin. Neurophysiol. 124 (5), 837–850.
Bentin, S., 1989. Electrophysiological studies of visual word perception, lexical organization, and semantic processing: A tutorial review. Lang. Speech 32 (3), 205–220.
Berron, D., van Westen, D., Ossenkoppele, R., Strandberg, O., Hansson, O., 2020. Medial temporal lobe connectivity and its associations with cognition in early Alzheimer's disease. Brain 143 (4), 1233–1248.
Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82 (4), 239–259.
Brier, M.R., Gordon, B., Friedrichsen, K., McCarthy, J., Stern, A., Christensen, J., Ances, B.M., 2016. Tau and Aβ imaging, CSF measures, and cognition in Alzheimer's disease. Sci. Transl. Med. 8 (338), 338ra66-338ra66.
Caputi, N., Di Giacomo, D., Aloisio, F., Passafiume, D., 2016. Deterioration of semantic associative relationships in mild cognitive impairment and Alzheimer Disease. Appl. Neuropsychol. Adult 23 (3), 186–195.
Cassani, R., Estarellas, M., San-Martin, R., Fraga, F. J., & Falk, T. H. (2018). Systematic review on resting-state EEG for Alzheimer's disease diagnosis and progression assessment. Disease markers, 2018.
Castañeda, M., Ostrosky-Solis, F., Pérez, M., Bobes, M.A., Rangel, L.E., 1997. ERP assessment of semantic memory in Alzheimer's disease. Int. J. Psychophysiol. 27 (3), 201–214.
Chan, A.S., Salmon, D.P., De La Pena, J., 2001. Abnormal semantic network for "animals" but not "tools" in patients with Alzheimer's disease. Cortex 37 (2), 197–217.
Chertkow, H., Whatmough, C., Saumier, D., Duong, A., 2008. Cognitive neuroscience studies of semantic memory in Alzheimer's disease. Prog. Brain Res. 169, 393–407.
David, J., Koessler, L., Rossion, B., 2023. A robust neural index of automatic generalization across variable natural views of familiar face identities. Vis. Cogn. 31 (8), 571–583.
de Partz MP BV, De Wilde V, Seron X, Pillon A (2001) LEXIS: Tests pour l'évaluation des troubles lexicaux chez la personne aphasique, Marseille.
Domoto-Reilly, K., Sapolsky, D., Brickhouse, M., Dickerson, B.C., Initiative, A.D.N., 2012. Naming impairment in Alzheimer's disease is associated with left anterior temporal lobe atrophy. Neuroimage 63 (1), 348–355.
Dorenkamp, M.A., Vik, P., 2018. Neuropsychological assessment anxiety: A systematic review. Pract. Innov. 3 (3), 192.
Ford, J.M., Askari, N., Gabrieli, J.D., Mathalon, D.H., Tinklenberg, J.R., Menon, V., Yesavage, J., 2001. Event-related brain potential evidence of spared knowledge in Alzheimer's disease. Psychol. Aging 16 (1), 161.
Frings, L., Kloppel, S., Teipel, S., Peters, O., Frolich, L., Pantel, J., Hull, M., 2011. Left anterior temporal lobe sustains naming in Alzheimer's dementia and mild cognitive impairment. Curr. Alzheimer Res. 8 (8), 893–901.
Garrard, P., Patterson, K., Watson, P.C., Hodges, J.R., 1998. Category specific semantic loss in dementia of Alzheimer's type. Functional-anatomical correlations from cross-sectional analyses. Brain J. Neurol. 121 (4), 633–646.
Gasser, M. (2004). The origins of arbitrariness in language. In Proceedings of the annual meeting of the Cognitive Science Society (Vol. 26, No. 26).
Giannakopoulos, P., Herrmann, F.R., Bussière, T., Bouras, C., Kövari, E., Perl, D.P., Hof, P., 2003. Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. Neurology 60 (9), 1495–1500.
Giffard, B., Desgranges, B., Eustache, F., 2005. Semantic memory disorders in Alzheimer's disease: clues from semantic priming effects. Curr. Alzheimer Res. 2 (4), 425–434.
Glosser, G., Friedman, R.B., Grugan, P.K., Lee, J.H., Grossman, M., 1998. Lexical semantic and associative priming in Alzheimer's disease. Neuropsychology 12 (2), 218.
Gold, G., Kövari, E., Corte, G., Herrmann, F.R., Canuto, A., Bussière, T., Giannakopoulos, P., 2001. Clinical validity of Aß-protein deposition staging in brain aging and Alzheimer disease. J. Neuropathol. Exp. Neurol. 60 (10), 946–952.
Grossman, M., Koenig, P., Glosser, G., DeVita, C., Moore, P., Rhee, J., Gee, J., 2003. Neural basis for semantic memory difficulty in Alzheimer's disease: an fMRI study. Brain 126 (2), 292–311.
Halgren, E., Dhond, R.P., Christensen, N., Van Petten, C., Marinkovic, K., Lewine, J.D., Dale, A.M., 2002. N400-like magnetoencephalography responses modulated by semantic context, word frequency, and lexical class in sentences. Neuroimage 17 (3), 1101–1116.
Heinrich, S.P., Mell, D., Bach, M., 2009. Frequency-domain analysis of fast oddball responses to visual stimuli: A feasibility study. Int. J. Psychophysiol. 73 (3), 287–293.
Hemptinne, C., Hupin, N., Lochy, A., Yüksel, D., Rossion, B., 2023. Spatial Resolution Evaluation Based on Experienced Visual Categories With Sweep Evoked Periodic EEG Activity. Invest. Ophthalmol. Vis. Sci. 64 (3), 17.
Hernández, M., Costa, A., Juncadella, M., Sebastián-Gallés, N., Reñé, R., 2008. Category-specific semantic deficits in Alzheimer's disease: a semantic priming study. Neuropsychologia 46 (4), 935–946.
Hodges, J.R., Salmon, D.P., Butters, N., 1992. Semantic memory impairment in Alzheimer's disease: failure of access or degraded knowledge? Neuropsychologia 30 (4), 301–314.
Hot, P., Rauchs, G., Bertran, F., Denise, P., Desgranges, B., Clochon, P., Eustache, F., 2011. Changes in sleep theta rhythm are related to episodic memory impairment in early Alzheimer's disease. Biol. Psychol. 87 (3), 334–339.
Iragui, V., Kutas, M., Salmon, D.P., 1996. Event-related brain potentials during semantic categorization in normal aging and senile dementia of the Alzheimer's type. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section 100 (5), 392–406.
Ivanoiu, A., Dricot, L., Gilis, N., Grandin, C., Lhommel, R., Quenon, L., Hanseeuw, B., 2015. Classification of non-demented patients attending a memory clinic using the new diagnostic criteria for Alzheimer's disease with disease-related biomarkers. J Alzheimers Dis 43, 835–847.
Ivnik, R.J., Smith, G.E., Lucas, J.A., Tangalos, E.G., Kokmen, E., Petersen, R.C., 1997. Free and cued selective reminding test: MOANS norms. J. Clin. Exp. Neuropsychol. 19 (5), 676–691.
Jack Jr, C.R., Albert, M.S., Knopman, D.S., McKhann, G.M., Sperling, R.A., Carrillo, M.C., Phelps, C.H., 2011. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7 (3), 257–262.
Jacova, C., Kertesz, A., Blair, M., Fisk, J.D., Feldman, H.H., 2007. Neuropsychological testing and assessment for dementia. Alzheimers Dement. 3 (4), 299–317.
Johansson, B., 1991. Neuropsychological assessment in the oldest-old. Int. Psychogeriatr. 3 (S1), 51–60.
Joubert, S., Brambati, S.M., Ansado, J., Barbeau, E.J., Felician, O., Didic, M., Kergoat, M. J., 2010. The cognitive and neural expression of semantic memory impairment in mild cognitive impairment and early Alzheimer's disease. Neuropsychologia 48 (4), 978–988.
Joyal, M., Groleau, C., Bouchard, C., Wilson, M.A., Fecteau, S., 2020. Semantic processing in healthy aging and Alzheimer's disease: a systematic review of the N400 differences. Brain Sci. 10 (11), 770.
Joyce, C.A., Gorodnitsky, I.F., Kutas, M., 2004. Automatic removal of eye movement and blink artifacts from EEG data using blind component separation. Psychophysiology 41, 313–325.

Jung, T.P., Makeig, S., Humphries, C., Lee, T.W., McKeown, M.J., Iragui, V., et al., 2000. Removing electroencephalographic artifacts by blind source separation. Psychophysiology 37, 163–178.
Katada, E., Sato, K., Ojika, K., Ueda, R., 2004. Cognitive event-related potentials: useful clinical information in Alzheimer's disease. Curr. Alzheimer Res. 1 (1), 63–69.
Kutas, M., Federmeier, K.D., 2011. Thirty years and counting: finding meaning in the N400 component of the event-related brain potential (ERP). Annu. Rev. Psychol. 62, 621–647.
Kutas, M., Hillyard, S.A., 1980. Reading senseless sentences: Brain potentials reflect semantic incongruity. Science 207 (4427), 203–205.
Laisney, M., Giffard, B., Belliard, S., de La Sayette, V., Desgranges, B., Eustache, F., 2011. When the zebra loses its stripes: Semantic priming in early Alzheimer's disease and semantic dementia. Cortex 47 (1), 35–46.
Lambon Ralph, M.A., Patterson, K., Hodges, J.R., 1997. The relationship between naming and semantic knowledge for different categories in dementia of Alzheimer's type. Neuropsychologia 35 (9), 1251–1260.
Lambon Ralph, M.A., Graham, K.S., Patterson, K., Hodges, J.R., 1999. Is a picture worth a thousand words? Evidence from concept definitions by patients with semantic dementia. Brain Lang. 70 (3), 309–335.
Lambon Ralph, M.A., Jefferies, E., Patterson, K., Rogers, T.T., 2017. The neural and computational bases of semantic cognition. Nat. Rev. Neurosci. 18 (1), 42–55.
Libon, D.J., Rascovsky, K., Powers, J., Irwin, D.J., Boller, A., Weinberg, D., Grossman, M., 2013. Comparative semantic profiles in semantic dementia and Alzheimer's disease. Brain 136 (8), 2497–2509.
Lochy, A., Van Belle, G., Rossion, B., 2015. A robust index of lexical representation in the left occipito-temporal cortex as evidenced by EEG responses to fast periodic visual stimulation. Neuropsychologia 66, 18–31.
Marinkovic, K., Dhond, R.P., Dale, A.M., Glessner, M., Carr, V., Halgren, E., 2003. Spatiotemporal dynamics of modality-specific and supramodal word processing. Neuron 38 (3), 487–497.
Melrose, R.J., Campa, O.M., Harwood, D.G., Osato, S., Mandelkern, M.A., Sultzer, D.L., 2009. The neural correlates of naming and fluency deficits in Alzheimer's disease: an FDG-PET study. International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences 24 (8), 885–893.
Meyer, P., Baeuchl, C., Hoppstädter, M., 2024. Insights from simultaneous EEG-fMRI and patient data illuminate the role of the anterior medial temporal lobe in N400 generation. Neuropsychologia 193, 108762.
Montanes, P., Goldblum, M.C., Boller, F., 1996. Classification deficits in Alzheimer's disease with special reference to living and nonliving things. Brain Lang. 54 (2), 335–358.
Moore, N.C., 1997. Visual evoked responses in Alzheimer's disease: a review. Clin. Electroencephalogr. 28 (3), 137–142.
Morgan, S.T., Hansen, J.C., Hillyard, S.A., 1996. Selective attention to stimulus location modulates the steady-state visual evoked potential. Proc. Natl. Acad. Sci. 93 (10), 4770–4774.
Morris, J.C., Mohs, R.C., Rogers, H., Fillenbaum, G., Heyman, A., 1988. Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. Psychopharmacol Bull 24, 641–652.
Mosconi, L., 2005. Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease: FDG-PET studies in MCI and AD. Eur. J. Nucl. Med. Mol. Imaging 32, 486–510.
Müller, M.M., Andersen, S., Trujillo, N.J., Valdes-Sosa, P., Malinowski, P., Hillyard, S., 2006. Feature-selective attention enhances color signals in early visual areas of the human brain. Proc. Natl. Acad. Sci. 103 (38), 14250–14254.
Nelissen, N., Vandenbulcke, M., Fannes, K., Verbruggen, A., Peeters, R., Dupont, P., Vandenberghe, R., 2007. Aβ amyloid deposition in the language system and how the brain responds. Brain 130 (8), 2055–2069.
Nelson, P.T., Alafuzoff, I., Bigio, E.H., Bouras, C., Braak, H., Cairns, N.J., Beach, T.G., 2012. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J. Neuropathol. Exp. Neurol. 71 (5), 362–381.
Nigam, A., Hoffman, J.E., Simons, R.F., 1992. N400 to semantically anomalous pictures and words. J. Cogn. Neurosci. 4 (1), 15–22.
Norcia, A.M., Appelbaum, L.G., Ales, J.M., Cottereau, B.R., Rossion, B., 2015. The steady-state visual evoked potential in vision research: A review. J. Vis. 15 (6), 4.
Olichney, J.M., Yang, J.C., Taylor, J., Kutas, M., 2011. Cognitive event-related potentials: biomarkers of synaptic dysfunction across the stages of Alzheimer's disease. J. Alzheimers Dis. 26 (s3), 215–228.
Ossenkoppele, R., Schonhaut, D.R., Schöll, M., Lockhart, S.N., Ayakta, N., Baker, S.L., Rabinovici, G.D., 2016. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 139 (5), 1551–1567.
Ossenkoppele, R., Smith, R., Ohlsson, T., Strandberg, O., Mattsson, N., Insel, P.S., Hansson, O., 2019. Associations between tau, Aβ, and cortical thickness with cognition in Alzheimer disease. Neurology 92 (6), e601–e612.
Ostrosky-Solís, F., Castañeda, M., Pérez, M., Castillo, G., Bobes, M.A., 1998. Cognitive brain activity in Alzheimer's disease: Electrophysiological response during picture semantic categorization. Journal of the International Neuropsychological Society 4 (5), 415–425.
Paitel, E.R., Samii, M.R., Nielson, K.A., 2021. A systematic review of cognitive event-related potentials in mild cognitive impairment and Alzheimer's disease. Behav. Brain Res. 396, 112904.
Passafiume, D., De Federicis, L.S., Carbone, G., Giacomo, D.D., 2012. Loss of semantic associative categories in patients with Alzheimer's disease. Appl. Neuropsychol. Adult 19 (4), 305–311.
Petit, D., Gagnon, J.F., Fantini, M.L., Ferini-Strambi, L., Montplaisir, J., 2004. Sleep and quantitative EEG in neurodegenerative disorders. J. Psychosom. Res. 56 (5), 487–496.
Polich, J., Corey-Bloom, J., 2005. Alzheimer's disease and P300: review and evaluation of task and modality. Curr. Alzheimer Res. 2 (5), 515–525.
Regan, D., 1966. Some characteristics of average steady-state and transient responses evoked by modulated light. Electroencephalogr. Clin. Neurophysiol. 20 (3), 238–248.
Regan, D., 1981. Evoked potential studies of visual perception. Canadian Journal of Psychology/Revue canadienne de psychologie 35 (2), 77.
Regan, D. (1989). Human brain electrophysiology. Evoked potentials and evoked magnetic fields in science and medicine.
Retter, T.L., Rossion, B., 2016. Uncovering the neural magnitude and spatio-temporal dynamics of natural image categorization in a fast visual stream. Neuropsychologia 91, 9–28.
Retter, T.L., Rossion, B., Schiltz, C., 2021. Harmonic amplitude summation for frequency-tagging analysis. J. Cogn. Neurosci. 33 (11), 2372–2393.
Revonsuo, A., Portin, R., Juottonen, K., Rinne, J.O., 1998. Semantic processing of spoken words in Alzheimer's disease: an electrophysiological study. J. Cogn. Neurosci. 10 (3), 408–420.
Rice, G.E., Lambon Ralph, M.A., Hoffman, P., 2015. The roles of left versus right anterior temporal lobes in conceptual knowledge: an ALE meta-analysis of 97 functional neuroimaging studies. Cereb. Cortex 25 (11), 4374–4391.
Rogers, T.T., Ivanoiu, A., Patterson, K., Hodges, J.R., 2006. Semantic memory in Alzheimer's disease and the frontotemporal dementias: a longitudinal study of 236 patients. Neuropsychology 20 (3), 319.
Rossion, B., 2014. Understanding individual face discrimination by means of fast periodic visual stimulation. Exp. Brain Res. 232, 1599–1621.
Rossion, B., Boremanse, A., 2011. Robust sensitivity to facial identity in the right human occipito-temporal cortex as revealed by steady-state visual-evoked potentials. J. Vis. 11 (2), 16.
Rossion, B., Retter, T.L., Liu-Shuang, J., 2020. Understanding human individuation of unfamiliar faces with oddball fast periodic visual stimulation and electroencephalography. Eur. J. Neurosci. 52 (10), 4283–4344.
Rouleau, I., Salmon, D.P., Butters, N., Kennedy, C., McGuire, K., 1992. Quantitative and qualitative analyses of clock drawings in Alzheimer's and Huntington's disease. Brain Cogn 18, 70–87.
Salmon, D.P., Butters, N., Chan, A.S., 1999. The deterioration of semantic memory in Alzheimer's disease. Canadian Journal of Experimental Psychology/Revue canadienne de psychologie expérimentale 53 (1), 108.
Salthouse, T.A., 2007. Implications of within-person variability in cognitive and neuropsychological functioning for the interpretation of change. Neuropsychology 21 (4), 401.
Schretlen, D.J., Munro, C.A., Anthony, J.C., Pearlson, G.D., 2003. Examining the range of normal intraindividual variability in neuropsychological test performance. J. Int. Neuropsychol. Soc. 9 (6), 864–870.
Silveri, M.C., Daniele, A., Giustolisi, L., Gainotti, G., 1991. Dissociation between knowledge of living and nonliving things in dementia of the Alzheimer type. Neurology 41 (4), 545.
Šoškić, A., Jovanović, V., Styles, S.J., Kappenman, E.S., Ković, V., 2022. How to do better N400 studies: reproducibility, consistency and adherence to research standards in the existing literature. Neuropsychol. Rev. 32 (3), 577–600.
Stothart, G., Smith, L.J., Milton, A., Coulthard, E., 2021. A passive and objective measure of recognition memory in Alzheimer's disease using Fastball memory assessment. Brain 144 (9), 2812–2825.
Tarawneh, H.Y., Mulders, W.H., Sohrabi, H.R., Martins, R.N., Jayakody, D.M., 2021. Investigating auditory electrophysiological measures of participants with mild cognitive impairment and Alzheimer's disease: A systematic review and meta-analysis of event-related potential studies. J. Alzheimers Dis. 84 (1), 419–448.
Teunissen, C.E., Verberk, I.M., Thijssen, E.H., Vermunt, L., Hansson, O., Zetterberg, H., Del Campo, M., 2022. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. The Lancet Neurology 21 (1), 66–77.
Thompson, P.M., Hayashi, K.M., De Zubicaray, G., Janke, A.L., Rose, S.E., Semple, J., Toga, A.W., 2003. Dynamics of gray matter loss in Alzheimer's disease. J. Neurosci. 23 (3), 994–1005.
Van der Linden M CF, Poitrenaud J, Kalafat M, Calicis, F WC, Adam S, et les membres du GREMEM (2004) L'épreuve de rappel libre/rappel indicé à 16 items (RL/RI16) In L'évaluation des troubles de la mémoire : Présentation de quatre tests de mémoire épisodique (avec leur étalonnage), Solal, ed., Marseille.
Vecchio, F., Babiloni, C., Lizio, R., Fallani, F.D.V., Blinowska, K., Verrienti, G., Rossini, P. M., 2013. Resting state cortical EEG rhythms in Alzheimer's disease: toward EEG markers for clinical applications: a review. Suppl. Clin. Neurophysiol. 62, 223–236.
Vettori, S., Dzhelyova, M., Van der Donck, S., Jacques, C., Steyaert, J., Rossion, B., Boets, B., 2019. Reduced neural sensitivity to rapid individual face discrimination in autism spectrum disorder. NeuroImage: Clinical 21, 101613.
Villemagne, V.L., Pike, K.E., Chételat, G., Ellis, K.A., Mulligan, R.S., Bourgeat, P., Rowe, C.C., 2011. Longitudinal assessment of Aβ and cognition in aging and Alzheimer disease. Ann. Neurol. 69 (1), 181–192.
Vogel, A., Gade, A., Stokholm, J., Waldemar, G., 2005. Semantic memory impairment in the earliest phases of Alzheimer's disease. Dement Geriatr Cogn Disord. 19 (2–3), 75–81.
Volfart, A., Rice, G.E., Ralph, M.A.L., Rossion, B., 2021. Implicit, automatic semantic word categorisation in the left occipito-temporal cortex as revealed by fast periodic visual stimulation. Neuroimage 238, 118228.
Wechsler, D. (1945). Wechsler memory scale.
Whitwell, J.L., Przybelski, S.A., Weigand, S.D., Knopman, D.S., Boeve, B.F., Petersen, R. C., Jack Jr, C.R., 2007. 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. Brain 130 (7), 1777–1786.

Wierenga, C.E., Stricker, N.H., McCauley, A., Simmons, A., Jak, A.J., Chang, Y.L., Bondi, M.W., 2011. Altered brain response for semantic knowledge in Alzheimer's disease. Neuropsychologia 49 (3), 392–404.
Yan, X., Goffaux, V., Rossion, B., 2022. Coarse-to-fine (r) automatic familiar face recognition in the human brain. Cereb. Cortex 32 (8), 1560–1573.
Zhang, F., Zhong, R., Li, S., Fu, Z., Wang, R., Wang, T., Le, W., 2019. Alteration in sleep architecture and electroencephalogram as an early sign of Alzheimer's disease preceding the disease pathology and cognitive decline. Alzheimers Dement. 15 (4), 590–597.
Zhou, H., Melloni, L., Poeppel, D., Ding, N., 2016. Interpretations of frequency domain analyses of neural entrainment: periodicity, fundamental frequency, and harmonics. Front. Hum. Neurosci. 10, 274.